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THE PROGNOSTIC VALUE OF CD10 IN PATIENTS WITH B-ACUTE LYMPHOBLASTIC LEUKEMIA: 10-YEAR EXPERIENCE

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ABSTRACT

Determination of prognostic factors in patients with acute leukemia is crucial in reducing intensive chemotherapy, decreasing economic costs, and improving the outcome of the patients. We conducted this study to determine the prognostic value of CD10 expression in B-acute lymphoblastic leukemia (studying the relationship between CD10 expression and therapeutic response, overall survival, and event-free survival). Also, we want to study the combined expression of CD10 and CD34, and the effect on overall survival and event-free survival. A retrospective study included 119 patients from 1st January 2010 to 31 December 2016. We monitored the patients until 1st December 2019. In B-acute lymphoblastic leukemia, expression of CD10 was 81.5%. Most patients whose Blasts had CD10+ were children and standard risk stratification. In contrast, patients with CD10- had significantly an increased incidence of B symptoms, fever (infection), and cerebrospinal fluid infiltration. We found that complete remission after 4 weeks and after 18 months of starting treatment was significantly higher in CD10+ patients than CD10- patients and in CD10+ and/or CD34+ patients than CD10-CD34- patients. Death was significantly higher in patients with CD10- than CD10+. The median survival rate was higher in patients with CD10+ than CD10- and in CD10+ and\or CD34+ patients than CD10-CD34- patients but without statistical significance. Our findings suggest that CD10 expression and the combined expression of CD10 and CD34 have a favorable prognosis in patients with B-acute lymphoblastic leukemia.

KEYWORDS: Acute leukemia, improving survival, Immunophenotyping, CD10, CD34.

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a neoplastic disorder that is rapidly fatal if untreated. [1] It is the most common malignancy in childhood and rare leukemia in adults.[2] Immunophenotyping is an essential part of the modern diagnostic and prognostic work-up of acute leukemia.[3] The prognostic factors are useful for risk stratification to identify patients who require more intensive therapy and stem cell transplantation in 1st complete remission (CR).[2]

Cluster of differentiation CD10, neprilysin, common acute lymphoblastic leukemia antigen (CALLA), neutral endopeptidase (NEP), enkephalinase, or EC 3.4.24.11 is a 90–110 kDa cell surface type II integral membrane protein of M13 family.[4] CALLA is a common zinc-dependent metalloendoprotease that inactivates several signaling peptides.[5] Numerous studies have demonstrated that CD10 is transiently present during B-cell maturation at early-B and pre-B lymphoblastic stages.[6] Scientists discovered the diagnostic and prognostic value of CD10 in ALL with the elaboration of rabbit antisera against leukemic cells. The common ALL (CALLA) antiserum (later named CD10) was further shown to react with leukemic cells from more than 80% of non-T-cell ALL patients but not with normal hematopoietic cells.[5] Even though its expression in some cases is related to better treatment response, CD10 expression is biased towards cancer proliferation and progression. CD10 can be a very useful progression marker and an attractive molecular target for targeted therapy designing. This behavior suggests that CD10 behaves as a dual-edge sword and depending upon the peptides present in the tumor microenvironment modulates cancer progression accordingly.[4]

CD10 is a surface marker that has been reported to have prognostic value in ALL, but the results were conflicting.[7,8,9,10,11] To clarify the importance of CD10 expression as an independent prognostic factor in B-ALL, we studied CD10 expression and the combined expression of CD10 and CD34 and linked them with the results. The absence of local studies prompted us to carry out this research to achieve practical benefits for patients.

MATERIALS AND METHODS

We carried out this study to determine the prognostic value of CD10 expression in B-ALL (studying the relationship between CD10 expression and therapeutic response, overall survival, and event-free survival). Besides, we want to study the combined expression of CD10 and CD34, and the effect on OS and EFS. A retrospective study included 119 B-ALL patients who were admitted to the center of chemotherapy from 1st January 2010 to 31 December 2016. We followed up the patients until 1st December 2019. Exclusion criteria were: patients with secondary ALL, patients who received prior chemotherapy or radiation, and patients with mature B-ALL. We excluded 35 patients; 23 patients didn't perform flow cytometry at diagnosis, 6 patients had mature B-ALL, two patients had secondary ALL from Non-Hodgkin lymphoma, a patient had secondary ALL from chronic lymphocytic leukemia, a patient had secondary ALL from chronic myeloid leukemia and two patients died before performing flow cytometry. We treated the included patients with protocols that applied at our center. Patients or their guardians provided written informed consent to participate in the study.

Definitions

Studied variables included age, gender, white blood cells (WBC), hemoglobin (HGB), platelets (PLT), risk stratification for children, CD10 expression, and CD34 expression. CD10 expression was positive when >20% and negative when ≤20%. [12] For CD34 expression, a 20% threshold was selected to identify positive cases. We determined risk stratification according to age, WBC, cytogenetic, central nervous system positive leukemia, and time to respond to induction therapy. The outcome was calculated as overall survival and event-free survival. Treatment response was defined as complete remission, induction failure, minimal residual disease (MRD), relapse, and death. OS was calculated from the first day of starting treatment to date of death or date of interrupted follow-up. EFS was calculated from the date of starting treatment to date of the first event: induction failure, MRD, relapse, death, or date of interrupted follow-up. A complete remission defined as the absence of leukemic cells in the peripheral blood and cerebrospinal fluid (CSF), less than 5% in bone marrow, and the absence of extracellular infiltration. MRD was defined as a presence of leukemic cells in bone marrow $>1 \times 10^{-3}$ after Induction, and $>5 \times 10^{-4}$ after Early Consolidation.

Statistical analysis

Descriptive Statistics: We used frequencies and percentages for qualitative variables, and measures of central tendency for quantitative variables.

Inferential Statistics: We used the Chi-square test to study the relationship between qualitative variables. Survival analysis (overall survival and event-free survival) was performed by using Kaplan-Meir curves. The hazard ratio was estimated by using univariate cox-regression. The initial variables were tested using the log-rank test, and groups were compared by using the log-rank test. Results were statistically significant when p-value <0.05. The program (IBM SPSS statistics) version19 was adopted to calculate statistical transactions and analyze results.

RESULTS

B-ALL patients were 119 patients (78.30%), and T-ALL patients were 33 patients (21.70%). Our study included 119 B-ALL patients, males were 66 patients (55.4%) and females were 53 patients (44.6%). The male to female ratio was 1.2:1. The median age was 8 years. CD10 antigen expressed in 97 patients (81.5%), CD10+ and/or CD34+ expression were found in 109 patients (91.6%).

When we compared between CD10+ group and CD10- group in terms of demographic distribution (gender, age), we didn't find statistical significance for gender, while 66% of CD10+ group were children, and the most common age group is 1 to <10 years age group (p=0.001) (Table 1). The comparison between two groups (CD10+, CD10-) according to clinical symptoms yielded statistical significance concerning the presence of B symptoms (p=0.04), fever (infection) (p=0.03) as well as CSF infiltration (p=0.03) that were more associated with CD10- group than CD10+ group. When we compared between two groups according to laboratory findings, we observed that 66% of patients with CD10+ had WBC $<30 \times 10^9$ /liter. In positive CD10 expression, we found that the relative frequency of standard risk stratification (SR) was significantly higher (p=0.001) (73% of 63 patients) than high-risk stratification (HR) (27% of 63 patients) (Table 1).

After 4 weeks of starting treatment we observed that 92.8% of patients with CD10+ went to CR, while 9.1% of patients with CD10- had MRD, contrariwise, 0% of patients with CD10+ had MRD (p=0.04). Furthermore, after 18 months of starting treatment 61.1% of CD10+ patients went to CR, while 46.2% of CD10- patients achieved CR (p=0.03). Death in CD10- group was significantly higher than CD10+ group, 54.9% versus 36.7% respectively (p=0.04) (Table 2).

Table 1: Clinical features of 119 B-ALL patients according to CD10 expression.

Variable	CD10+ N 97 (%)	CD10- N 22 (%)	N 119 (%)	P-value
B symptoms	45 (46.4)	15 (68.2)	60 (50.4)	**0.04**
Splenomegaly	42 (43.3)	14 (63.6)	56 (47.1)	0.06
Hepatomegaly	41 (42.3)	13 (59.1)	54 (45.4)	0.1
Fever (infection)	26 (26.8)	11(50)	37 (31.1)	**0.03**
Lymphadenopathy	28 (28.9)	8 (36.4)	36 (30.3)	0.3
Hemorrhage	12 (12.4)	5 (22.7)	17 (14.3)	0.2
CSF infiltration	0 (0)	1 (4.5)	1 (8)	**0.03**
Gender Male Female	56 (57.7) 41 (42.3)	10 (45.5) 12 (54.5)	66 (55.5) 53 (44.5)	0.3
Age 1 - <10 <1 & ≥ 10 to 13 >13 – <30 ≥30 – <60 ≥60	58 (59.8) 6 (6.2) 21 (21.6) 11 (11.3) 1 (1)	4 (18.2) 2 (9.1) 5 (22.7) 7 (31.8) 4 (18.2)	62 (52.1) 8 (6.7) 26 (21.8) 18 (15.1) 5 (4.2)	**0.001**
WBC × 10^9/liter <30 ≥30	64 (66) 33 (34)	13 (59.1) 9 (40.9)	77 (64.7) 42 (35.3)	0.6
HGB g/L <50 50 – 100 ≥100	9 (9.3) 67 (69.1) 21 (21.6)	0 (0) 17 (77.3) 5 (22.7)	9 (7.6) 84 (70.6) 26 (21.8)	0.3
PLT × 10^9/liter <20 20-100 ≥100	20 (20.6) 60 (61.9) 17 (17.5)	3 (13.6) 13 (59.1) 6 (27.3)	23 (19.3) 73 (61.3) 23 (19.3)	0.5
Risk stratification (only in children) Standard Risk High Risk	N 63 (%) 46 (73) 17 (27)	N 6 (%) 4 (66.7) 2 (33.3)	N 69 (%) 50 (72.5) 19 (27.5)	0.7

Abbreviations. CD, Cluster of Differentiation; HGB, Hemoglobin; PLT, Platelets; WBC, White Blood Cells.

Table 2: Outcome of 119 B-ALL patients according to CD10 expression.

Outcome ¶	CD10+ N 97 (%)	CD10- N 22 (%)	N 119 (%)	P-value
After 4 weeks CR Failure MRD Death	90 (92.8) 6 (6.2) 0 (0) 3 (3.1)	19 (86.4) 1 (4.5) 2 (9.1) 0 (0)	109 (91.6) 7 (5.9) 2 (1.7) 3 (2.5)	**0.04**
Within 18 months CR Relapse MRD Death	62 (66) 29 (30.8) 2 (2.1) 12 (12.8)	13 (59.1) 8 (36.4) 0 (0) 7 (31.8)	75 (64.7) 37 (31) 2 (1.7) 19 (15.9)	0.2
After 18 months CR Relapse Death	44 (61.1) 28 (38.9) 15 (20.8)	6 (46.2) 6 (46.2) 3 (23.1)	50 (58.8) 34 (28.6) 18 (15.1)	**0.03**

¶ *Outcome was calculated from the first day of starting treatment.*
Abbreviations. CD, Cluster of Differentiation; CR, Complete Remission; MRD, Minimal Residual Disease.

By comparison between CD10+ and/or CD34+ group and CD10-CD34- group, we found that CR after 4 weeks of starting treatment was higher in CD10+ and/or CD34+ group (92.7%) than CD10-CD34- group (80%), per contra, 20% of CD10-CD34- group went to MRD versus 0% of CD10+ and/or CD34+ group (p=0.02). Also, after 18 months of starting treatment we noted that 60.3% of CD10+ and/or CD34+ group obtained CR, however

42.9% of CD10-CD34- group obtained CR (P=0.008). Death was additionally higher in CD10-CD34- group (48.6%) than CD10+ and/or CD34+ group (39.3%) but without statistical significance (Table 3).

Table 3: Outcome of 119 B-ALL patients according to CD10 and/or CD34 expression.

Outcome ¶	CD10-CD34- N 10 (%)	CD10+ and/or CD34+ N 109 (%)	N 119 (%)	P-value
After 4 weeks CR Failure MRD Death	8 (80) 0 (0) 2 (20) 0 (0)	101 (92.7) 7 (6.4) 0 (0) 3 (2.7)	109 (91.6) 7 (5.9) 2 (1.7) 3 (2.5)	**0.02**
Within 18 months CR Relapse MRD Death	7 (70) 3 (30) 0 (0) 2 (20)	68 (64.2) 34 (32.1) 2 (1.9) 17 (16.1)	75 (64.7) 37 (31) 2 (1.7) 19 (15.9)	0.8
After 18 months CR Relapse Death	3 (42.9) 3 (42.9) 2 (28.6)	47 (60.3) 31 (39.7) 16 (20.5)	50 (42) 34 (28.6) 18 (15.1)	**0.008**

¶ *Outcome was calculated from the first day of starting treatment.*
Abbreviations. CD, Cluster of Differentiation; CR, Complete Remission; MRD, Minimal Residual Disease.

In all patients, OS at 3 years was 71.4% (85 patients); also, the mean of OS was 3.9±2.8 years. The mean of EFS was 3.3±2.7 years. At the end of the study, death was observed in 33.7% (40 patients) and OS was 66.3% (79 patients). In univariate analysis for OS and EFS, CD10 and the combined expression of CD10 and CD34 had no statistical significance (Table 4).

Table 4. Univariate cox-regression analysis of overall survival and event-free survival in 119 B-ALL patients.

CD10 , CD34	n	OS			EFS		
		HR	CI 95%	P-value	HR	CI 95%	P-value
CD10 Positive Negative	 97 22	 1 1.6	 [0.8 – 3.4]	 0.4	 1 1.8	 [0.8 – 3.7]	 0.1
CD10 and CD34 CD10+and/orCD34+ CD10-CD34-	 109 10	 1 1.2	 [0.4 – 2.1]	 0.7	 1 1.4	 [0.5 – 4.1]	 0.3

Abbreviations. CD, Cluster of Differentiation; CI, Confidence Interval; EFS, Event Free Survival; HR, hazard ratio; OS, Overall Survival.

Kaplan-Meier analyses for OS in all patients and children alone showed that expression of CD10 had a better outcome, but didn't reach significance. Median of survival time in all patients was 7.2±0.4 years for CD10+ patients versus 5.6±0.9 years for CD10- patients (Figure 1A), and in children alone was 7.9±0.4 years for CD10+ patients versus 6.3±1.9 years for CD10- patients (Figure 1B).

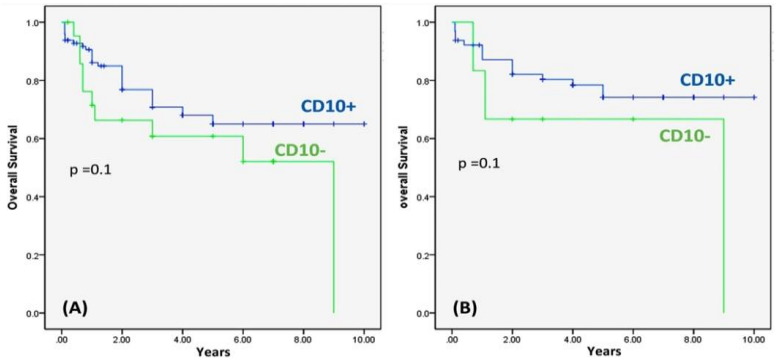

Figure 1: Overall survival (OS) in B-ALL patients according to CD10 expression. (A) OS in 119 patients, Log-rank=0.1. (B) OS in children (69 patients), Log-rank=0.1. Abbreviations: CD, Cluster of Differentiation.

Kaplan-Meier analyses for OS in all patients showed that expression of CD10+ and/or CD34+ had better outcomes than CD10-CD34- expression but without statistical significance. The median of survival time in all patients was 6.9±0.4 years for CD10+ and/or CD34+ patients instead of 5.1±0.8 years for CD10-CD34- patients (Figure 2).

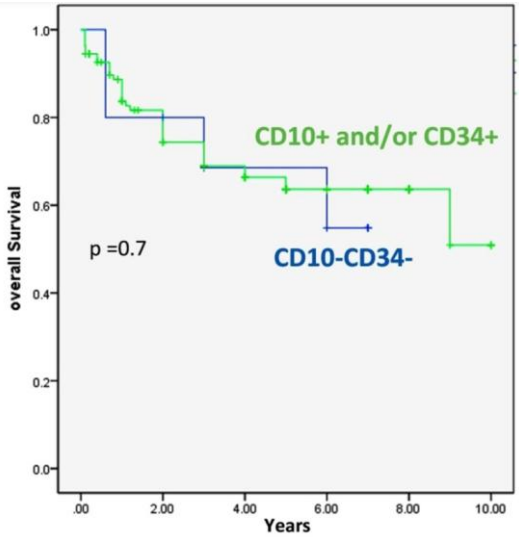

Figure 2: Overall survival in 119 B-ALL patients according to CD10 and/or CD34 expression, Log-rank =0.7. Abbreviations: CD, Cluster of Differentiation.

DISCUSSION

In B-ALL, CD10 expression diverges between studies and ranges from 76 to 97.1%.[8,9,11] When we compared between CD10+ group and CD10- group in terms of demographic distribution (gender, age), we didn't find statistical significance for gender, and this corresponds to other studies.[13,14] Authors found that most CD10+ pre-B-ALL patients were between 1-9 years old,[14] also, in our study we found that 59.8% of CD10+ patients were between 1 - <10 years old. Furthermore, we detected that 72.7% of CD10- patients were adults, and this compatible with Kumar *et al*. who found that most CD10- group were adults. [15] Previous studies showed that ALL prognosis for the elderly was worse than pediatric patients. [16] Authors found that the lack of CD10 expression in B-lineage ALL was significantly associated with CNS involvement, [7] and this compatible with our study. Attarbaschi *et al.* demonstrated that 77% of CD10+ Pre B-ALL patients had WBC <20 $\times 10^9$ /liter with statistical significance, moreover 91% of CD10+ Pre B-ALL patients had significantly WBC <50 $\times 10^9$ /liter. [14] Leukocyte counts are an important prognostic factor for achieving a CR and for remission duration. [17] In positive CD10 expression we demonstrated that the relative frequency of SR stratification was significantly higher (73% of 63 patients) than HR stratification. Supriyadi *et al.* found that in B-ALL the relative frequency of positive CD10 expression was higher in SR stratification (83% of 94 patients) than in HR stratification, but without statistical significance.[11] Consolini *et al*. observed that CD10 antigen was significantly associated with standard risk inclusion (p=0.0001), besides, high-risk patients fared statistically worse than standard-risk patients.[7]

After 4 weeks of starting treatment, we observed that 92.8% of patients with CD10+ went to complete remission, Amritha Malini G *et al*. found that 92.6% of CD10 positive cases were in remission.[20] We noted that 9.1% of patients with CD10- had MRD, contrariwise, 0% of patients with CD10+ had MRD (p=0.04), Li *et al.* demonstrated that there were no residual lymphoid cell subpopulations with a stable or increased percentage in the CD10+ populations.[21] After 18 months of starting treatment the rate of CR decreased, but still significantly higher in CD10+ group, per contra, death was significantly higher in CD10- group. In Kaplan-Meier analysis, Supriyadi *et al.* found that patients with CD10 expression had a better prognosis, but without statistical significance,[11] and this compatible with our study as well as a study of Dakka *et al*.,[8] and a study of Boucheix *et al*.[22] This can be explained by CD10 positive acute lymphoblastic leukemia cells were cycling cells with elevated c-myc levels and propensity to apoptosis, whereas CD10 negative acute lymphoblastic leukemia cells had lower cycling capacities and c-myc levels, and were resistant to apoptosis in vitro.[23] For B-ALL, hyperdiploidy was associated with expression of CD10 (100%),[8] while CD10- Pre B-ALL in adults is characterized by a high MLL rearrangement rate and a worse outcome.[24] Studies performed on multiple organs and cell types indicate that the enzyme downregulates induced responses to peptide hormones.[25] Along B-cell ontogeny this enzyme participates in the regulation of stromal cell-dependent B-cell lymphopoiesis.[26] It is supposed that the enzyme may hydrolyze a peptide that promotes the initial proliferation of early lymphoid progenitors or cleaves a peptide precursor and generates a break-down product that inhibits early lymphoid development.[27]

By comparison between CD10+ and\or CD34+ group and CD10-CD34- group, we noted that CR after 4 weeks and after 18 months of starting treatment was significantly higher in CD10+ and\or CD34+ group than CD10-CD34- group, Amritha Malini G *et al.* and Dakka *et al*. detected the same results.[20,8] In Kaplan-Meier analysis, patients with CD10+ and\or CD34+ expression had better survival than CD10-CD34- expression, but without statistical significance, Supriyadi *et al.* found that the lack of both CD10 and CD34 expression was related to a worse prognosis especially in T-ALL.[11] At the end of our study, OS for all patients was 66.3% and death was 33.7%. Rytting *et al.* noted that OS at 5 years for patients between 13-39 years old was 60%,[28] and Ribera *et al*. found that OS at 6 years for patients between 15-30 years old was 69%.[29] Aziz *et al.* found that death for all children and adult patients was 34.5%,[9] and this corresponds with our results.

CONCLUSIONS

In our population of children and adults with B-ALL, we found that CD10+ expression associated with ages between 1 - <10 years old, WBC <30 $\times 10^9$ /liter, and SR stratification, while CD10- expression associated with B symptoms, fever (infection) and CSF infiltration. CR and OS were better in CD10+ patients than CD10- patients, whilst MRD was higher in CD10- patients. Thus, CD10 expression and its combination with CD34 expression may have a better prognosis in patients with B-ALL.

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LIST OF ABBREVIATIONS

B-ALL: B-acute lymphoblastic leukemia; CALLA: Common acute lymphoblastic leukemia antigen; CD: Cluster of Differentiation; CR: Complete remission; CNS: Central nervous system; CSF: Cerebrospinal fluid; EFS: Event-free survival; HGB: Hemoglobin; OS: Overall survival; PLT: Platelets; WBC: White blood cells; MRD: Minimal residual disease; SR: Standard-risk stratification; HR: High-risk stratification.

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